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EXAMINER	
CLOW, LORI A	
ART UNIT	**PAPER NUMBER**
1631	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/595,580	Applicant(s) DOUGHERTY ET AL.	
	Examiner Lori A. Clow, Ph.D.	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54 and 61-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-54 and 61-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's arguments have been considered and are not deemed to be fully persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 1-54 and 61-67 are currently pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-54 and 61-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. ***This is a new matter rejection.***

Applicant argues that the specification provides for the "effectiveness" language with the following passage:

> The nonlinear model predicts gene expression among the set of genes. The effectiveness of the nonlinear model in predicting gene expression can then be measured to quantify relatedness for genes in the set (page 3, lines 7-10).

The claim language still reads on quantification equating to effectiveness of predicting gene expression rather than effectiveness of the model being used to predict gene relatedness, as stated in the specification. Applicant points out on page 7, line 17 of the response filed 2 June

2003 that "the claim does not recite predicting gene expression *per se*", further confusing the issue of claim language verses disclosure teachings.

Claim 54 still does not have support in the instant specification. There is no indication of gene relatedness being quantified in the disclosure. The above passage, cited by Applicant, does not rectify the problem and does not explain quantification of the effectiveness as it pertains to gene relatedness. At best it provides support for quantification of the gene expression.

Claims 1-54 and 61-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and similar claims (36, 47, 50, 54, and 61) are unclear in that step (a) and step (c) do not relate to step (b) which is predicting gene expression. How does step (b) relate to the testing of the "effectiveness" of a non-linear model? The claim steps do not fulfill the steps in the preamble which are to quantify gene relatedness. The application of effectiveness in the claims is still unclear. To have an effect on something means to act on or create a response. Perhaps applicant means "accuracy". As recited in the claims, it is unclear how measuring the effectiveness creates a prediction of gene expression?

Claim 1 also recites "a plurality of selected **permutations** of the plurality of candidate genes" and then goes on to say in step (a) "constructing a nonlinear model predicting gene expression for **the permutation**." This lacks antecedent basis.

Claims 4 and 5 are unclear because it is unclear whether the recited limitations are method steps or are functional limitations of the nonlinear model. Applicant must make this clear by providing positive limitations to said claims.

Claims 7 and 10 are unclear in that "measuring effectiveness" is defined as comparing observed gene expression to gene expression predicted by the nonlinear model?" which is in contradiction to the effectiveness being a quantification of gene relatedness as defined in the amended claims.

Claim 8 is confusing in that "constructing" generally means to build something by concrete steps, as in a model and in the art does not equate to choosing something.

Claim 9 is unclear in that it does not agree with step (c) of claim 1 in that step (c) is directed to measuring the effectiveness where effectiveness is a quantitation and in claim 9 measuring is directed to evaluating the model to estimate a coefficient of determination for an optimal model estimated by the model. How is a model's effectiveness determined by the model itself?

Claim 11 recites the limitation "the data" instead of "data". There is insufficient antecedent basis for this limitation in the claim.

Claim 12 is unclear for the reasons stated above with regards to claim 1 . How does effectiveness equate to "quantification of gene relatedness?"

Claim 14 is unclear in that the method appears to be circular. How is effectiveness predicted on gene relatedness if said relatedness is measured on effectiveness?

Claims 15 and 16 are unclear in that how is a "contribution" determined?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 29 and 30 remain rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. (J. Biomed. Optics (1997) Vol. 4, No. 4, pages 364-374).

As applied to claims 29-30, Chen et al. disclose that the technology of microarray analysis is particularly useful for direct comparisons of mRNA levels from various cell types (page 365). Comparison of gene expression levels is achieved by taking ratios of average expression levels for individual genes and the observed differences of expression ratios is determined (see abstract). Nonlinear predictors are utilized to predict expression levels of target genes based upon expression levels of other genes, as illustrated on page 369, column 1, second paragraph). Furthermore, coefficients of determination, exemplified in Chen et al. as constant coefficients of variance, are used in this determination (see page 369, column 2). Finally genes are ranked based upon likelihood of relatedness, as exemplified in Table 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102 (e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33-35 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (Journal of Biomedical Optics (1997) vol. 2:364-373: PTO-1449 reference) in view of Chen et al. (Proc. SPIE (1999) vol.3602:422-428; PTO-1449 reference) in further view of Jian et al. (IEEE Transactions on Pattern Analysis and Machine Intelligence (2000) vol. 22:4-37: PTO-1449 reference)

Chen et al. disclose that the technology of microarray analysis is particularly useful for direct comparisons of mRNA levels from various cell types (page 365). This requires the ability to discern subtle changes in expression levels. This is best accomplished by pixel selection

methods based on the Mann-Whitney test (page 368). The three points to this test are: (1) association of confidence levels with every intensity measurement based upon significance; (2) real-time measurements; and (3) lack of need for normality assumptions. In essence, data is randomly generated over the set of possible data. This reveals relationships between gene positions on the microarray (as described in detail on page 368). Target are aligned, averaged, and subjected to a threshold. After several iterations of these permutations, the result is deemed a site of significance. Once gene expression is established, expression ratios are determined for the differing samples or sets of genes. Finally, ratios are analyzed via statistical means (generation of confidence levels etc.) in order to obtain a satisfactory result. To verify this result, the method of K clustering is used (as described in Chen et al. (Proc. SPIE (1999) vol.3602:422-428; PTO-1449 reference). Chen et al. disclose a method of clustering genes based upon gene expression in order to identify functional relationships between the genes of interest (see abstract, page 422). This method utilizes cDNA microarrays and and is performed on a computer. "Gene expression patterns for a given biological process for a plurality of inputs representing expression at different time points are obtained ($i=1, 2, ...n$). Each gene pattern consists of expression ratios from m genes. The gene expression ration vector (m) contains n components. Therefore, the expression vectors must be partitioned into K clusters (C_1, $C_2, ...C_k$), such that cluster C_j contains m_j genes and each gene is in exactly one cluster." (page 423, point 2.) This is put simply on page 424, which explains the preparation and partitioning of gene expression data. This method is applied to gene expression data conducted in yeast (*S. cerevisiae*) containing 6400 distinct cDNA. Genes with no significant expression level changes were eliminated from the study, because they are usually housekeeping genes that do not respond

to experimental manipulations or they are genes that cannot be detected in microarray systems. Other systems were tested, as well, using the similar clustering approach as for the yeast (multidimensional scaling analysis) to establish relatedness amongst different gene expression patterns. This approach is certainly applicable to a variety of inputs that serve as predictors for the method. These could include particular cell states, as well as external stimuli, as is well known in the art of microarray analysis (differential displays etc...) (see page 422, introduction, 3rd paragraph). This method can be used with a plurality of predictive inputs, representative of differential expression between two or more samples of biological material and this can be done to compare predicted to observed levels (page 423, study example, top of page). Furthermore, the study shows that this method is useful for not only tens of thousands of genes, but also useful for a subset of those genes (a fingerprint). Another important factor in this method is that these levels of expression are statistically analyzed to give the "best" prediction possible across a set of biological samples (page 423, 2nd paragraph).

The above analysis of microarray gene expression based upon comparisons between pluralities of gene expression patterns can be useful in the prediction of gene relatedness when incorporating neural network technology as taught by Jian et al. Jian et al., as applied to claims 33-35, define "pattern" as consisting of two tasks: (1) supervised classification in which an input pattern is identified as a member of a predefined class and (2) unsupervised classification (e.g. clustering) in which the pattern is assigned to a hitherto unknown class. The four known approaches to pattern recognition are: (1) template matching, (2) statistical classification, (3) syntactic or structural matching, and (4) neural networks. These models are not necessarily independent (page 5). The definitions of the above four are well known in the art.

In the instant application, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Chen I and II et al. with neural network technology, as described in Jian et al. As Jian states, the most common neural network system for pattern classification is the feed-forward network, which includes multiplayer perceptron and Radial-Basis Function (page 7). These provide a suite of nonlinear algorithms for feature extraction and classification. In addition, these feature extractions and classifications can be mapped on neural architectures. Inherent in neural networking is the use of statistical pattern recognition calculations, which are usually hidden from the user (internal manipulations). It is well known in the art that neural networks consist of a test pattern and a training pattern, meeting all of the limitations of the instant claims. For instance in the training mode, the feature extraction/selection module finds the appropriate features (like gene expression patterns) for representing the input patterns and the classifier is trained to partition the feature space. In the classification mode, the trained classifier assigns the input pattern to one of the pattern classes under consideration based upon measured features (page 8), as outlined in the instant application. Without further describing the vast information available in the field of neural networks, the motivation to analyze gene expression patterns is clearly put forth in Chen et al. (Proc SPIE) on page 425 in which they state, "expression clustering results provide group statistical information which may ultimately lead biologists to better understanding of the gene functional behavior during a given biological process....The future research work will certainly include an implementation combined with the gene expression database connection....in order to provide more efficient way towards unknown gene understanding."

Applicant argues that Chen I, Chen II are directed to gene relatedness and not gene expression levels, as in claim 1. However, the relied upon art is still applicable to claims 33-35 which do read on gene expression analysis. Applicant further states that the action attacks claim 1 by assembling references to show that predicting gene expression is obvious. In response to Applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Chen II (Proc. SPIE (1999)), clearly disclose that future work with the disclosed gene expression profiles will include implementation combined with gene expression databases etc. in order to provide more efficient ways of understanding unknown genes (page 428). Furthermore, Jian clearly states that the neural network systems described have far reaching capabilities and have implications in a vast array of fields, such as bioinformatics and data mining (page 4, column 2 and Table 1). Therefore, it would have been prima facie obvious to combine gene expression analysis with the technology of neural networking, as in the instant invention.

No claims are allowed.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242, or (703) 308-4028.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday-Friday from 10am to 6:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Legal Instrument Examiner, Tina Plunkett, whose telephone number is (703) 305-3524, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

MARJORIE MORAN
PATENT EXAMINER

August 15, 2003
Lori A. Clow, Ph.D.
Art Unit 1631